15. (amended) A method of inhibiting the expression of insulin-like growth factor binding protein 5 in cells or tissues comprising contacting said cells or tissues *in vitro* with the antisense compound of claim 1 so that expression of insulin-like growth factor binding protein 5 is inhibited.

REMARKS

Claims 1-20 are pending in the instant application. Claims 1-20 have been rejected. Claims 11 and 16-20 have been canceled. Claims 1, 3, and 15 have been amended. No new matter has been added by these additions and amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 15-20 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these

being enabling for antisense inhibition of human insulin-like growth factor binding protein 5 expression *in vitro* does not reasonably provide enablement for *in vivo* antisense inhibition of this gene expression; the Examiner cites several articles on the technology of antisense to support this position. Applicants respectfully traverse this rejection of the claims.

Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* is highly unpredictable.

The Examiner has pointed to six articles and a press release on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

The paper by Crooke is a review paper on the basic principles of antisense therapeutics. The statements alluded to by the

predictions about *in vivo* pharmacokinetic behavior are only one small part of this review paper. When read in its entirety the author is merely stating a well known fact in the development of any drug, not merely antisense. Pharmacokinetics is not the study of the pharmacological activity of an agent, such as is studied commonly in cells, but rather the study of the biological distribution of a drug in an animal or human. Therefore, the statements by the author do not demonstrate the unpredictability of antisense oligos *in vivo* but rather merely state the obvious, that one would not use studies on cellular uptake to predict pharmacokinetics in animals or humans because it is not a logical use of such data for any drug. Data in cells are used routinely, however, as predictors of pharmacological activity in animals and humans. It is a fundamental principle of drug development that data from whole cell studies, such as are provided in Example 15 of the instant specification, are directly applicable to predicting in vivo activity. The teachings of the paper by Crooke and the other cited review paper (Branch) provide no reason to doubt that this fundamental principle is applicable to antisense agents.

In fact, statements in the paper by Crooke support the fact

product in terms of applying the basic principles of pharmacology. For example, on page 22, first paragraph, Crooke points out "...numerous well-controlled [pharmacological] studies have been reported in which antisense activity was conclusively demonstrated [*in vitro*]." The key according to Crooke is the careful design of the *in vitro* studies to carefully evaluate dose-response relationships and antisense mechanism, similar to the type of studies presented in the instant specification. Therefore, what this paper, and the other cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

Moreover, the paper by Brown (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data

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The paper by Palu et al. (1999) is a review paper on the technology of gene therapy, not antisense. Gene therapy is an entirely different technology with its own set of issues for drug development. Citing this paper to support the unpredictability of antisense is inappropriate. Nowhere does this paper state that extrapolation from *in vitro* data on antisense compounds to *in vivo* effects is unpredictable.

The paper by Agrawal and Kandimalla (2000) is another review paper on the technology of antisense. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Chirila et al. (2000) is a review of the use of polymers for delivery of antisense compounds. Although this paper reviews problems that have arisen during development of antisense, problems that are addressed and solved in the specification as filed, nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

Finally, the press release cited by the Examiner does not support the conclusion that data from in vitro studies is not [illegible] in vivo activity. This failure of a clinical trial

be statistically significantly better than a placebo on a particular endpoint. It does not mean the drug was without activity to inhibit gene expression when results from *in vitro* studies are extrapolated to *in vivo* activity.

However, Applicants have amended claim 15 to recite that the method is performed *in vitro* in an earnest effort to advance the prosecution and facilitate the allowance of this case. Claims 16-20 have been canceled with Applicants reserving the right to file a continuing application directed to this subject matter without prejudice. Withdrawal of the rejection is requested in light of these amendments.

II. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1, 2, 4, 5, 11, 12, 14 and 15 have been rejected under 35 U.S.C. 102(b) as being anticipated by Hayn et al. (1996). The Examiner suggests that this reference discloses 8-50 nucleobase antisense compounds that inhibit an active site on a nucleic acid molecule encoding insulin-like growth factor binding protein 5 and inhibition of this gene in cells, as well as pharmaceutical compositions and phosphorothioate linkages. Applicants

At the outset, Applicants have amended claim 1, and by dependency claims 2-15, to refer to antisense compounds that target specific nucleobase regions of insulin-like growth factor binding protein 5 nucleic acid molecules that are taught in the instant invention. Support for those amendments can be found throughout the specification as filed but in particular at pages 83-85.

Huynh et al. (1996) disclose use of a 21 mer phosphorothioate antisense oligonucleotide that is complementary to nucleotides 813-834 of a human insulin-like growth factor binding protein 5 nucleic acid molecule (corresponding to SEQ ID NO: 10) and its use to inhibit gene expression in breast cancer cells in culture. Nowhere does this paper teach or suggest antisense compounds that target the nucleobase regions of the insulin-like growth factor binding protein 5 nucleic acid molecules as now claimed. Accordingly, this paper fails to teach the limitations of the claims as amended and cannot anticipate the instant invention (MPEP 2131). Withdrawal of this rejection is respectfully requested.

Claims 1-5 and 11-15 have been rejected under 35 U.S.C. 102(b) as being anticipated by Melore et al. (2000). The Examiner [illegible] this paper [illegible] antisense between 8 and 50

inhibition of this gene in cells, as well as an oligonucleotide that aligns with SEQ ID NO: 13 of the instant application. Applicants respectfully traverse this rejection.

Melone et al. (2000) discloses a 15 mer phosphorothioate antisense oligonucleotide complementary to a region of the mRNA encompassing the start codon of human insulin-like growth factor binding protein 5 and its use to inhibit gene expression and show that this protein acts as a diffusible factor to sequester insulin-like growth factors and other growth factors to down-regulate Duchenne muscular dystrophy myoblast proliferation. Nowhere does this paper teach or suggest antisense compounds that target the nucleobase regions of the insulin-like growth factor binding protein 5 nucleic acid molecules as now claimed. Accordingly, this paper fails to teach the limitations of the claims as amended and cannot anticipate the instant invention (MPEP 2131). Withdrawal of this rejection is respectfully requested.

Claims 1, 2, 4, 5, 11, 12 and 14-19 have been rejected under 35 U.S.C. 102(a) as being anticipated by Miyake et al. (2001). The Examiner suggests that this paper discloses intraperitoneal [illegible] antisense oligonucleotide

compounds are modified as claimed and comprise a pharmaceutically compatible carrier. Claims 1, 2, 4, 5 and 11-19 have been rejected under 35 U.S.C. 102(b) as being anticipated by Miyake et al. (2000). The Examiner suggests that this paper, by the same authors as the 2001 paper, discloses *in vitro* administration of the same compositions used above *in vivo*. The Examiner suggests that the 2000 paper discloses antisense that aligns with SEQ ID NO's 14, 16, 17, 19, 21 and 25 of the instant invention. Applicants respectfully traverse these rejections over the Miyake references.

Miyake et al. (2001) is a review paper that describes the same antisense compounds as are disclosed by Miyake et al. (2000). Miyake et al. (2000) discloses an 18 mer antisense oligonucleotide complementary to the translation initiation site of mouse insulin-like growth factor binding protein 5 mRNA and its use to inhibit mRNA expression. Nowhere do these papers teach or suggest antisense compounds that target the nuclease regions of the insulin-like growth factor binding protein 5 nucleic acid molecules as now claimed. Accordingly, these papers fail to teach the limitations of the claims as amended and cannot anticipate the [illegible] of these rejections is

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Claims 1, 2, 3, 11 and 15 have been rejected under 35 U.S.C. 102(b) as being anticipated by Pavco et al. (WO 99/50403). The Examiner suggests that this patent application discloses antisense oligonucleotides that target and specifically hybridize with an active site of insulin-like growth factor binding protein 5 and inhibit its expression *in vitro*. The Examiner points to alignments with SEQ ID NO's 31 and 32 of the instant application. Applicants respectfully disagree with the Examiner's suggestion.

Pavco et al. disclose ribozymes targeted to a number of RNA targets, including integrin beta 3. As shown in the sequence alignment provided by the examiner, SEQ ID NO: 31 of the instant invention is identical over 15 consecutive nucleotides with the integrin beta 3 substrate mRNA (i.e., target) sequence shown as SEQ ID NO: 6360 in Pavco. Since SEQ ID NO: 31 of applicant's invention is an antisense oligonucleotide sequence, the fact that it is identical to the integrin beta 3 mRNA sequence is irrelevant. Nowhere does Pavco teach antisense oligonucleotides which target and specifically hybridize with an active site of a nucleic acid encoding IGFBP5. Also as shown in the sequence alignment provided [illegible] of the instant invention is

Pavco. Since SEQ ID NO: 32 of applicant's invention is an antisense oligonucleotide sequence, the fact that it is identical to the integrin beta 3 mRNA sequence is again irrelevant. Nowhere does Pavco teach antisense oligonucleotides which target and specifically hybridize with an active site of a nucleic acid encoding IGF-BPs. Accordingly, this patent application fails to teach the limitations of the claims and cannot anticipate the instant invention (MPEP 2131). Withdrawal of this rejection is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Miyake et al., Pavco et al., Huynh et al., and Malone et al., as applied to claims 1-5 and 11-15 above, and further in view of McKay et al. (US Patent 5,877,309). The Examiner suggests that it would have been prima facie obvious to one of ordinary skill to design antisense compounds to target insulin-like growth factor binding protein 5 and inhibit its expression based on the teachings of Miyake et al., Pavco et al., [illegible] as claimed

teachings of McKay et al. Applicants respectfully traverse this rejection.

At the outset, claim 1 and its dependent claims have been amended to now claim antisense compounds targeted to specific regions of nucleic acid molecules encoding insulin-like growth factor binding protein 5, excluding regions taught by cited references. Support for these amendments to the claims can be found throughout the specification as filed.

The primary references cited by the Examiner have been discussed in detail *supra*. Nowhere do these references teach or suggest antisense compounds targeted to insulin-like growth factor binding protein 5 nucleic acid molecules as now claimed. Further, nowhere do these references, when combined, teach the sequences as now listed in the amended claims. Therefore, the primary references cited fail to teach the limitations of the claims as amended.

The secondary reference cited fails to overcome the deficiencies in teaching of the primary references.

McKay et al. (US Patent 5,877,309) disclose development of [illegible] does this reference

as now claimed. Therefore, this reference fails to overcome the deficiencies in teaching of the primary references.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims as amended, which claim antisense compounds targeted to specific regions of nucleic acid molecules encoding insulin-like growth factor binding protein 5, and thus cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

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Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

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Registration No. 32,257

Date: January 21, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 11 and 16-20 have been canceled without prejudice.

Claims 1, 3 and 15 have been amended as follows:

1. (amended) A compound 6 to 50 nucleobases in length targeted to ~~the start codon, the~~ nucleobases 65 through 84, nucleobases 299 through 361, nucleobases 503 through 516, or nucleobases 518 through 728 of a coding region, ~~the~~ nucleobases 996 through 1205, or nucleobases 1579 through 1598 of a 3' untranslated region of a nucleic acid molecule (SEQ ID NO: 3) encoding insulin-like growth factor binding protein 5, nucleobases 11 through 30 or nucleobases 584 through 603 of a nucleic acid molecule (SEQ ID NO: 10) encoding insulin-like growth factor binding protein 5, an intron or an intron/exon junction region of a nucleic acid molecule (SEQ ID NO: 11) encoding insulin-like growth factor binding protein 5, or nucleobases 197 through 216 of a 3' untranslated region of a nucleic acid molecule (SEQ ID NO: 12) encoding insulin-like growth factor binding protein 5, wherein said compound specifically ~~hybridizes with a nucleic acid molecule encoding insulin-like~~

~~The compound of claim 1~~

3. (amended) The compound of claim 2 wherein the antisense compound has a sequence comprising SEQ ID NO: ~~13,~~ 14, 15, 16, 17, 18, 19, 21, 23, 24, 25, 26, 27, 28, 29, 30, ~~31, 32,~~ 33, 34, 35, 36, 38, 39, 40, 41, 42 or 43.

15. (amended) A method of inhibiting the expression of insulin-like growth factor binding protein 5 in cells or tissues comprising contacting said cells or tissues *in vitro* with the antisense compound of claim 1 so that expression of insulin-like growth factor binding protein 5 is inhibited.

CERTIFICATE OF TRANSMISSION BY FACSIMILE (37 CFR 1.8) Applicant(s): Susan M. Freier			Docket No. RTS-0253
Serial No. 09/975,123	Filing Date October 9, 2001	Examiner J. Zara	Group Art Unit 1635

Invention: ANTISENSE MODULATION OF INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 5 EXPRESSION

I hereby certify that this Notification of a Change in Status
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.:	RTS-0253
Inventors:	Susan M. Freier
Serial No.:	09/975,123
Filing Date:	October 9, 2001
Examiner:	J. Zara
Group Art Unit:	1635
Title:	Antisense Modulation of Insulin-Like Growth Factor Binding Protein 5 Expression

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On January 21, 2003

Jane Massey Licata Registration No. 32,257

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

NOTIFICATION OF A CHANGE IN STATUS

Applicant hereby provides notification that the status of the above-identified application is changed to Large Entity.

The extension of time fee transmitted herewith is paid at the Large Entity rate.

Respectfully submitted,

Jane Massey Licata
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January 21, 2003

TO GROUP: 1635

FAX NUMBER: 1-703-872-9306

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NUMBER OF PAGES: 25
(including this sheet)

MESSAGE: Attached is a response to the Office Action dated August 19, 2002, a Notification of a Change in Status, Petition for Extension of Time (2 months) and authorization to charge deposit account 50-1619 in the amount of $410.00 for extension of time fee.

URGENT! PLEASE DELIVER IMMEDIATELY UPON RECEIPT. THANK YOU!

☼ ☼ ☼ ☼ ☼ ☼ ☼ ☼ ☼ ☼ ☼ ☼ ☼ ☼ ☼ ☼ ☼

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